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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
RAO, MANJUNATH N	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 12/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/855,320	BAYER, ROBERT	
	Examiner	Art Unit	
	Manjunath N. Rao, Ph.D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 November 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6,8,10-17,19-36,38,40,42-49,51-55,66-68,70-77 and 79-106* is/are pending in the application.

4a) Of the above claim(s) *22-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4, 6, 8, 10-17, 19-21, 31-36, 38, 40, 42-49, 51-55, 66-68, 70-77, 79-106* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

In view of the agreement made by the Examiner during the interview with the applicants (held on 11-2-05), the finality of the previous Office action mailed on 3-14-05 has been withdrawn. A new non-final Office action now follows.

Claims 1-4, 6, 8, 10-17, 19-36, 38, 40, 42-49, 51-55, 66-68, 70-77, 79-106 are currently pending and are present for examination. Claims 1-4, 6, 8, 10-17, 19-21, 31-36, 38, 40, 42-49, 51-55, 66-68, 70-77, 79-106 are now under consideration. Claims 22-30 remain withdrawn from consideration as being drawn to non-elected invention.

Currently claims 1, 8, 10-17, 19, 20, 21, 31-33, 40, 42, 43-49, 51, 52, 53, 70-74, 79-86 and 94 are all directed to a method for modifying the glycosylation pattern of a glycopeptide using exclusively a first fucosyltransferase wherein said first fucosyltransferase is eukaryotic, lacks a membrane anchoring domain and is a member selected from FT-IV, V, VI, VII and combinations thereof.

Claims 54-55, 87-93, 95-106 are drawn to large-scale method for modifying the glycosylation pattern of a glycopeptide comprising contacting the glycopeptide with a first fucosyltransferase (FT), wherein the FT enzyme can be any FT from any source and has no limitation regarding its membrane anchor domain.

Claims 2, 3, 4, 6, 34-36, 38, 66-68, 75-77 are all directed to a method for modifying the glycosylation pattern of a glycopeptide using a first fucosyltransferase wherein said first fucosyltransferase is eukaryotic, lacks a membrane anchoring domain and is a member selected from FT-IV, V, VI, VII and combinations thereof and wherein the glycopeptide comprises a

second acceptor moiety for a second FT and method comprises contacting the reaction mixture with a second FT such that the glycopeptide has a substantially uniform fucosylation pattern.

Applicants' arguments made during the interview on 11-2-05 as well as the arguments filed on 5-18-05 and the signed Declaration by Dr. Bayer on 6-13-05, have all been fully considered and are deemed to be persuasive to overcome the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. Specifically Examiner has partially withdrawn the rejection under 35 U.S.C. 103(a) in view of the applicant's arguments. However, Examiner has reinstated the previously made rejections under 35 U.S.C. 112, 1st paragraph in view of the arguments presented by the applicants to overcome the obviousness rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 6, 8, 10-17, 19-21, 31-36, 38, 40, 42-49, 51-53, 66-68, 70-77, 79-86 and 94 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a general method of modifying the glycosylation pattern of a glycopeptide using a fucosyltransferase (FT) such as FucT-IV, V, VI, or VII comprising an acceptor moiety and a donor moiety on a glycopeptide such that the glycopeptide is fucosylated, does not reasonably provide enablement for such a method for modifying the glycosylation pattern of a glycopeptide using exclusively a first fucosyltransferase wherein said first fucosyltransferase is eukaryotic,

lacks a membrane anchoring domain and is a member selected from FT-IV, V, VI, VII and combinations thereof and optionally using a second fucosyltransferase (without any limitation regarding its transmembrane domain) to fucosylate a second fucosylation site, wherein the glycopeptide is substantially uniformly fucosylated, or at least 80% of the acceptor moieties on the glycopeptide are fucosylated, or wherein a recombinant glycopeptide is substantially identically fucosylated as the wild type (non-recombinant) glycopeptide. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 1-4, 6, 8, 10-17, 19-21, 31-36, 38, 40, 42-49, 51-53, 66-68, 70-77, 79-86 and 94 are so broad as to encompass a method of using any fucosyltransferase or any FucT-IV, V, VI, or VII including mutants, variants and recombinants. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the use of extremely large number of enzymes broadly encompassed by the claims and furthermore because of the characteristic nature of fucosyltransferases to altogether lose their specific ability to transfer fucose when the transmembrane domain in removed. Because of this unique characteristic nature of fucosyltransferases and also due to the fact that the amino acid sequence of a protein determines

its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity, it requires a knowledge of and guidance with regard to which specific fucosyltransferase can be used in the above method without its transmembrane domain as well as which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to those fucosyltransferase enzymes lacking transmembrane domain and specifically have the properties of substantially uniformly fucosylating a glycopeptide, or at least fucosylating 80% of the acceptor moieties on the glycopeptide, or is capable of fucosylating a recombinant glycopeptide substantially identical to the wild type (non-recombinant) glycopeptide. While fucosyltransferases are known and available in the art, enzymes endowed with above properties are not. Therefore it would require undue experimentation of the skilled artisan to make and use any fucosyltransferase for the above claimed method. The specification is limited to teaching the method using, perhaps specific variants or mutant FTs which are capable of above activities but provides no guidance with regard to the making of such variants and mutants or with regard to identifying such variants. In view of the great breadth of the claim, amount of experimentation required to make the claimed polypeptides, the lack of guidance, working examples, and unpredictability of the art in predicting function from a polypeptide primary structure (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), the claimed invention would require undue

experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the polypeptides encompassed by this claim.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility for use in the above method are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass the use of any FTs because the specification does not establish: (A) that any FT lacking transmembrane domain can be used in the above method; (B) regions of the protein structure which may be modified in order to obtain an enzyme having above special activity; (C) the general tolerance of FTs to modification and extent of such tolerance; (D) a rational and predictable scheme for modifying any amino acid residues in any FT with an expectation of obtaining the desired biological function; and (E) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including all or any FTs or any variants with an enormous number of amino acid modifications. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient

guidance, determination of FTs having the desired biological characteristics for the above method is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Examiner notes that in response to the above rejection in one of the previous Office action (see Office action mailed on 6-9-04), applicants had argued that FTs are well known in the art and any FT can be used by those skilled in the art in order to carry out the above method. In response to such vehement arguments, Examiner withdrew the above rejection and rejected the claims under obviousness rejection arguing that it would have been obvious to one of ordinary skill in the art to remove the transmembrane domain and use such FTs in the above method. In response to such an obviousness rejection, applicants themselves pointed out that not all FT can be modified and used for the above method since it is well known in the art that removal of the transmembrane domain completely changes the final activity of certain FTs and referred to the references of Costa et al. and Natsuka et al. which the Examiner has used in the obviousness rejections. Applicants held on to their argument that because of the teachings of Costa et al. and/or Natsuka et al. not any or all FTs can indeed be used for the method as Examiner had argued in his obviousness rejection and demanded that Examiner address the anomaly noted in the art (i.e., the references of Costa and Natsuka et al.). In view of the references of Costa et al. and Natsuka et al. somewhat teaching away and also introducing the ambiguity that removal of transmembrane domain leads to loss of specific activity in a FT, Examiner has withdrawn his obviousness rejection, however, has brought back this enablement rejection.

Claims 1-4, 6, 8, 10-17, 19-21, 31-36, 38, 40, 42-49, 51-53, 66-68, 70-77, 79-86 and 94 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-4, 6, 8, 10-17, 19-21, 31-36, 38, 40, 42-49, 51-53, 66-68, 70-77, 79-86 and 94 are directed to a method of fucosylation using polypeptides lacking transmembrane domain and further having the properties of substantially uniformly fucosylating a glycopeptide, or at least fucosylating 80% of the acceptor moieties on the glycopeptide, or is capable of fucosylating a recombinant glycopeptide substantially identical to the wild type (non-recombinant) glycopeptide, or is capable of large-scale fucosylation of a glycopeptide. Claims 1-4, 6, 8, 10-17, 19-21, 31-36, 38, 40, 42-49, 51-53, 66-68, 70-77, 79-86 and 94 are rejected under this section of 35 USC 112 because the claims are directed to a method of use of a genus of polypeptides including modified polypeptide sequences, modified by at least one of deletion, addition, insertion and substitution of an amino acid residue that have not been disclosed in the specification. No description has been provided of the polypeptide sequences encompassed by the claim. No information, beyond the characterization of the polypeptides as fucosyltransferases or fucosyltransferases lacking membrane anchor domain, has been provided by applicants which would indicate that they had possession of the claimed genus of polypeptides. The specification does not contain any disclosure of the structure of all the polypeptide sequences, including fragments and variants within the scope of the claimed genus. The genus of polypeptides claimed is a large variable genus including peptides which can have a wide variety of structures. Therefore many structurally unrelated polypeptides are encompassed within the scope of these claims. The specification discloses only a single species of the claimed genus which is insufficient to put one of skill in the art in possession of the attributes and

features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that applicant had possession of the claimed invention at the time the instant application was filed.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

In response to one of the previous Office action, applicant has traversed the above rejection arguing that claims are drawn to a method of use of fucosyltransferases and as claims are not directed to the product, fucosyltransferases and since the applicant adequately describes the method of use of FTs, the written description requirement is satisfied. Applicants also referred to the court decision *In re Herschler* whose fact pattern applicant argues is identical to the instant claims. Applicants argued that the Office rejected claims for lack of written description for not disclosing a representative number of physiologically active steroids in an invention which claimed the use of DMSO to enhance the delivery of physiologically active steroids and the CCPA reversed the Office's rejection reasoning that because the invention was not directed to novel steroids, explicit disclosure of all steroidal agents was not required to meet written description. Based on such a reasoning, applicants argued that there is no requirement of written description in the instant case as well. Examiner respectfully disagreed then and disagrees now with such an argument. This is because, contrary to the above court case, applicant claims a method wherein not any FT can be used but specific FTs lacking transmembrane domain and capable of substantially uniformly fucosylating a glycopeptide, or at least fucosylating 80% of the acceptor moieties on the glycopeptide, or is capable of fucosylating a recombinant glycopeptide substantially identical to the wild type (non-recombinant) glycopeptide, or is capable of large-scale fucosylation of a glycopeptide. While several FTs are known in the art, not all such FTs have the above functional properties (see

argument in the enablement rejection above). Therefore, applicants need to provide the written description of FTs that are needed for practicing the above method. Without a written description one skilled in the art cannot reasonably conclude that applicant had possession of such enzymes to practice the claimed invention at the time the instant application was filed. Therefore the above rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 54-55, 87-93, 95-106, are rejected under 35 U.S.C. 103(a) as being unpatentable over Seed et al. (WO 96/40881, 12-19-1996), or Kashem et al. (US 5,374,655, 12-20-1994), and Paulson et al. (WO 98/31826, 7-23-1998). Claims 54-55, 87-93, 95-106, of the instant application are drawn to a large-scale method of modifying glycosylation pattern of a glycopeptide comprising an acceptor moiety or producing a recombinant glycopeptide having a fucosylation pattern that is substantially identical to a fucosylated glycopeptide having a known fucosylation pattern comprising contacting *in vitro* at least 500 mg of glycopeptide with a reaction mixture containing fucose donor moiety and a first fucosyltransferase only or further with a second fucosyltransferase wherein the fucosyltransferase enzymes comprise FucT-IV, V, VI or VII, wherein said enzymes are bacterial in nature and wherein the glycopeptide is a fragment, a hormone etc., on a cell or immobilized on a column etc. and wherein the glycopeptide is contacted by a glycosyltransferase other than an FucT, under appropriate

conditions to transfer fucose from the donor to acceptor such that the glycopeptide has a substantially uniform fucosylation pattern and terminating the reaction when the fucosylation pattern is obtained.

Kashem et al. and Seed et al. teach a similar method of modifying the glycosylation pattern by fucosylating a polypeptide (which when considered broadly would encompass glycopeptides as well) using a eukaryotic FucT-III fucosyltransferase enzyme produced recombinantly. The reference of Seed et al. also provides sources for other fucosyltransferases such as FucT-IV and FucT-VII (see page 2). The reference does not specifically a large-scale method.

Paulson et al. teaches methods for *in vitro* sialylation of recombinant glycoproteins. The reference essentially teaches a method of glycosylation involving an enzyme other than a fucosyltransferase.

Combining the teachings of the above references, along with the common knowledge in the art regarding enzyme immobilization and affinity chromatography etc. it would have been obvious to those skilled in the art, to alter the method of fucosylation of a polypeptide as taught by Kashem et al. or Seed et al. by using a fucosyltransferase as taught by said references and produce a recombinant glycopeptide having a fucosylation pattern that is substantially identical to a fucosylated glycopeptide having a known fucosylation pattern --either with a single enzyme or with more than one of the above enzymes either by using them simultaneously or sequentially--, that is already glycosylated (sialylated) as taught by Paulson(b) et al. by incubating the reaction under such conditions and time such that a recombinant glycopeptide having a fucosylation pattern that is substantially identical to a fucosylated glycopeptide having a

known fucosylation pattern is produced. It would be well within the skills of those artisans in the art to extend the incubation time or add extra enzyme or manipulate the immobilized columns such that the method can be converted to a large-scale method wherein resulting glycopeptide is fucosylated. It would also be well within the skills of those artisans of the art to constantly monitor the fucosylation pattern by sampling process during the reaction and terminate the reaction when the pattern of fucosylation is substantially identical to that seen on the reference glycopeptide. One of ordinary skill in the art would be motivated to do so as Seed et al. teach that fucosylated proteins produce therapeutics useful for treatment of diseases such as adverse immune reaction. One of ordinary skill in the art would have a reasonable expectation of success since Kashem et al. and Seed et al. teach almost an identical system but not on a so called large-scale. Also, one of ordinary skill in the art would have a reasonable expectation of success since methods for immobilization of enzymes and affinity chromatography and methods to determine the amount of fucose groups on a given polypeptide are all well known and available to those skilled in the art.

Therefore, the above invention would have been *prima facie* obvious to one of ordinary skill in the art.

Conclusion

None of the claims are allowable.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Manjunath N. Rao, Ph.D. whose telephone number is 571-272-0939. The Examiner can normally be reached on 7.00 a.m. to 3.30 p.m. If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura

Achutamurthy can be reached on 571-272-0928. The fax phone numbers for the organization where this application or proceeding is assigned is 571-273-8300 for regular communications and for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Manjunath N. Rao, Ph.D.
Primary Examiner
Art Unit 1652

December 12, 2005